(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 711 546 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
15.05.1996 Bulletin 1996/20

(21) Application number: **94926248.9**

(22) Date of filing: **07.09.1994**

(51) Int. Cl.[6]: **A61K 9/00**

(86) International application number:
PCT/ES94/00084

(87) International publication number:
WO 95/31179 (23.11.1995 Gazette 1995/50)

(84) Designated Contracting States:
AT BE CH DE DK FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **17.05.1994 ES 9401078**

(71) Applicant: **LABORATORIOS CUSI, S.A.**
E-08320 El Masnou (Barcelona) (ES)

(72) Inventors:
- **LOPEZ CABRERA, Antonio**
  E-08018 Barcelona (ES)
- **TORRELLA CABELLO, Gemma**
  E-08320 El Masnou (Barcelona) (ES)
- **VALLET MAS, José Alberto**
  E-08022 Barcelona (ES)
- **BERGAMINI, Michael Van Wie**
  E-08320 El Masnou (Barcelona) (ES)

(74) Representative: **Ungria Lopez, Javier et al**
Avda. Ramon y Cajal, 78
E-28043 Madrid (ES)

(54) OPHTALMIC SOLUTION BASED ON DICLOFENAC AND TOBRAMICINE AND ITS APPLICATIONS

(57) The ophtalmic solution comprises (a) the equivalent to 0.001-0.14 % of Diclofenac itself or an isomer, or a derivative or one of the pharmaceuticaly acceptable salts thereof; (b) the equivalent to a value of 0.001-0.45 % of Tobramicine, obtained from Tobramicine itself or from an isomer or a derivative or one of its pharmaceutically acceptable salts thereof; (c) optionally a solubilizer, an isotonizer, a pH damper, a viscosizer, a chelator, a preserving agent, and/or an excipient for pharmaceutical hydrogels. Application to the treatment of ocular and otic inflammations and/or infections.

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Description

TECHNICAL FIELD OF THE INVENTION

The present invention is comprised within the technical field of formulations intended for the treatment of ocular and otic inflammation processes which are presented together with infections.

Specifically, the present invention offers a formulation based on Diclofenac and Tobramycin for its ophthalmic and otic topical use.

TECHNICAL BACKGROUND OF THE INVENTION

The non steroidal antiinflammatory drugs (AINE) were introduced in ophthalmic practice as an alternative to the corticosteroids. At present, it is considered that the efficacy of the available AINEs can be compared to the less potent corticoids with the advantage that they are to be found a priori, lacking some of the negative affects associated with the use of any corticoids, unfavourable influence in certain types of infections -viruses, fungii and tuberculosis- and an increase of the intraocular pressure.

The association of an antibiotic and an antiinflammatory drug in ophthalmic pharmacy has had a generally useful result in inflammations associated with infections of ocular front segments, specially in conjunctivitis. In fact, data exists on severe bacteriological etiology conjunctivities which shows that the association of a corticoid with an antibiotic was more effective than a single antibiotic in the inactivation of the disorder [(1) Leibowtiz HM. Human Conjunctivities II. Treatment. Arch. Ophthalmol. 1976; 94:175 2-6]. In this sense, it seems logical to think that the association of a type of antiinflammatory drug lacking the potential negative effects which are characteristic of the corticoids (for example, a AINE) with an antibiotic, may serve as therapeutical alternative.

It has also been observed that the surgical procedures of front segment (for example, cataracts operations) are frequently associated with a postoperative inflammation which is reduced if a non steroidal antiinflammatory drug is administered immediatly prior to the operation and is prolonged during the postoperative period [(Othenin-Girard PH Association diclofenacdexamethasone dans le traitement de 'inflammation postopératoire: étude prospective en double-insu Klin Mbl. Augenheilk 1992;200:362-66; (3) Shiow-Wen Liou. The effect of 0.1 % Indomethacin eyedrops on cataract surgery. J. Ocular Pharmacol. 1991; 7:7 7 -81; (4) Flach AJ. The effect of Ketorolac tromethamine in reducing postoperative inflammation:double-mask parallel comparison with Dexamethasone. Ann. Ophtalmol. 1989; 19:407-411]

A correlation has been described between the blefaroconjuntival microbian flora present in the preoperative cataracts surgery and the isolated germs of postoperative endophthalmitis [(5) Parke DW. Endophthalmitis. In: K.Tabbara Infections of the eye. Little Brown & Oc. 1st. Edition. 1986 Boston (U.S.A.)]. For this reason, there is an agreement between the authors to suitably sterilize the external ocular structures whilst there is a possibility of infection in the surgical wound. A possibility used in the general practice is the topic administration of antibiotics with the correct spectrum in the pre and postoperative period. The combination of a non steroidal antiinflammatory and of an antibiotic allows the approach to both aspects (inflammation and the possibility of infection).

From the previous description, it is make clear that the possibility of having available a combination of an antiinflammatory agent and an antibiotic may seem necessary from the therapeutical point of view. On consideration of steroidal antiinflammatory agents, formulations can be found in the International Market which combine the said compounds with antibiotics in general and with Tobramycin in particular [(6) Vademecum International (1993) : 34th Edition. Medicom; (7) physicians' Desk Reference for Ophthalmology (1994). 22nd Edition. Medical Economics Data]

The combination of a non steroidal antiinflammatory agent with antibiotics is not as documented as in the previous case, nor has any speciality containing the said associaton been commercialized. The Fu and Lidgate European Patent EP 0.390.071 Al is to be noted, which claims a preserving system for opthalmic solutions which allow the compatibility of non steroidal antiinflammatory agents, among others, the Detorolaco Trome-thamol and Diclofenac, with preservatives belonging to the quaternary ammonium group by means of a non ion surfactant, specifically a polyethoxilate octyl phenol and preferably the Octoxynol 40, in the presence of Tobramycin. According to the inventors, formulations proposed avoid the interaction established between the AINESs and the quaternary ammoniums. Similar proposals have been carried out for formulations which only present quaternary ammonium (Patents EP 0.306.98[illegible] USP 4.8 29.088). For some of these compounds, it has been established that the interaction is due to an ion formation among the carboxyl group of the antiinflammatory agents and the quaternary ammonium group [(8) Dreisen der Glas, S.M. and Bult. A. Incompatibility of indometacin and benzalkonium in eye drops due to ion-pair formatic Pharmacevtisch Weekblad Scientific Edition 1987;9:29-32; (9) Ogawa, T and Ohara, K. and Shimizu, H. Efects of Pretreatment with mydriatics on intraocular penetration of 0.1 % Pranoprofen. Jpn. J. Ophthalmol. 1993; 37:47-55]

When intending to develop a Diclofenac and Tobramycin ophthalmic formulation, some of the examples described in Patent EP 0.390.071 Al, have been reproduced. Consequently, when combining Tobramycin (0.3%) with tromethamol Ketorolac (0.5%) a clear and transparent solution has been obtained. However, when conducting the same experiment with the sodium Diclofenac (0.5%) it has been observed that it is impossible to obtain a clear and transparent solution,

observing solid particles without disolving. In both cases, the same process of elaboration has been used, the simple mixture of the components, such as is described in the example of Patent of Fu and Lidgate. The preparation, under the same conditions of single solutions with Tobramycin (0.3%) or with sodium Diclofenac (0.5%) has permitted to observe, that in the former case, a clear and transparent solutions has been obtained, whilst in the latter case, it has not been possible, a cloudy solution having been obtained. All the formulations has been studied with the same quantity (0.01%) of one of the quaternary ammoniums used in Ophthalmology, the Bensalconium Chloride (BAC). Solid particles without disolving have also been observed when preparing a formulation which includes a 0.1% of sodium diclofenac, which is the concentration generally used in ophthalmology. The presence of particles in suspension may be due to the follwoing reasons:

- The insolubility of the sodium Diclofenac under the experimental conditions used.
- The formation of an interaction between some of the disolution components, as for example, between the Diclofenac and the Tobramycin, since when elaborating the formulation which only includes the tobramycin as active principle, a clear and transparent solution is obtained.

Paying attention to the bibliographic data consulted [(10) Morimoto, Y., Hatanaka, T. and Sugibayashi, K. and Omiya, H. Prediction of Skin Permeability of Drugs: Comparison of Human and Hairless Rat Skin. J. Pharm. Pharmacol 1992; 44:634- 6 39; (11) Kriwet, K. and Müller-goymann, C. binary Diclofenac Diethylamine-water systems: Micelles, vesicle and lyotropic liquid crystals. Eur J.Pharm, Biopharm. 1993; 39 (6) :234-238] the first reason can be emphasized, since the work pH (7.4 ± 0.4), the Diclofenac, presents a greater solubility to the concentration used in the experiments.

With the object of confirming the second possibility, formulations have been prepared with 0.1% (concentration generally used in Ophthalmology) of sodium Diclofenac, a 0.3% of Tobramycin (concentration generally used in Ophthalmology), a 0.01% of BAC, a 1.0% of octoxynol 40 (maximum concentration claimed in Patent EP 0.390.071 A 1) and adjusting the pH to 8.0 (maximum value specified in Patent EP 0.390.071 A1). Two additional formulations have been prepared in parallel, one exclusively with sodium Diclofenac as active principle, and the other only with tobramycin as active principle. Samples of the three formualtions have been placed at 4 and 22°C in order to follow the evolution thereof under critical conditions, from the point of view of the appearance of precipitates (4°C), though realistic from the point of view of the conditions under which a preparation may be found during the life time of a pharmaceutical product, and under normal shelf-life conditions (22°C). In the case of the formulation with the two active principles, the appearance of precipitates have been observed in a time $\leq$ than 41 days, whilst in the other two formulations it has not been so. No appearance of precipitates have been observed at environmental temperature in any case whatsovever.

The precipitate formulated, has separated, and has been analyzed, with the detection in the same, of the presence of sodium Diclofenac and Tobramycin, both by Thin Layer Chromatography and HPLC and by I.R. spectrography. The IR spectrum of the precipitate shows characteristic bands of each one of the active principles which are not found in the spectrums of the individual components (see Figura 1). The DSC analysis of the precipitate shows a profile which is clearly differenciated from the one obtained with the individual components, as well as the profile obtained of the simple physical mixture of sodium Diclofenac and Tobramycin (see figure 2).

The appearance of precipitation in a time $\leq$ to 3 days has also been observed, even at 22°C, with a formulation which contains 0.15% of sodium diclofenac, 0.45% of tobramycin, 1.0% of Octoxynol 40 and to which the pH has been adjusted to 8. These concentrations have selected, which are included in the claims of Patent of Fu and Lidgate, due to the fact that it is considered that they are the maximums at which a formulation may be found with the normal concentrations of Diclofenac and Tobramycin in Ophthalmology, 0.1% and 0.3% respectively, considering the need of having specifications for the elaboration of the formulations, the potential requirement of overdoses of the same, complying with the stability of the molecules [(6) Vademecum International (1993). 34th Edition. Medicom; (12) U.S.P. XXII (1990). United States Pharmacopeial Convention, INC:; (13) Brandl, M. and Gu, L Degradation of Tobramycin in aqueous solution. Drug Development and Industrial Pharmacy, 1992; 18(3):1423-1436.] and to the concentration of the formulations by losses due to evaporation of the containers used generally with these products.

With the object of determining more widely, at which experimental conditions a clear and transparent solution cannot be obtained, a study has been conducted on the influence of the sodium Diclofenac concentration, the Octoxynol concentration and the pH in the combination of sodium Diclofenac-Tobramycin in the presence of BAC. As range for the sodium Diclofenac concentrations, values comprised within 0.05 and 0.5% have been selected, values which include the values generally used in ophthalmology and which are included in the concentrations claimed in Patent EP 0.390.071 Al. As Octoxynol concentrations, values comprised within 0.01 and 1.0% have been selected, this latter value being the one which corresponds with the maximum value claimed in Patent of Fu and Lidgate. The pH studied has been 6, 7 and 8, values which coincide with the ones specified in said Patent. The concentration of Tobramycin and BAC has been established in all cases at 0.3 and 0.01% respectively. The rest of the components have been set in all cases and have corresponded with the examples specified in Patent EP 0.390.071 Al. The initial experimental plan has corresponded with a factorial design 3^3 and as incidences have been observed, new formulations have been considered in order to limit the experimental conditions under which the formation of a clear and transparent solution containing sodium

Diclofenac and Tobramycin may be observed. When proceeding with the elaboration of the different formualtions and collection of the results, it was observed that the best conditions for the obtention of clear and transparent solutions are those which correspond to the most alkalininic pH from the ones studied and to the highest concentrations of surfactant. These facts manifest the contribution of the ion interaction, as well as with other AINEs and of hydrophobicals to the formation of the observed precipitate. It has been considered that with ph > 8, the Tobramycin is to been found in the majority of cases in the non ion form (14) which minimizes the electrostatic interaction.

After 30 days of storage in refrigerator, only clear and transparent solutions have been obtained under the following experimental conditions.

pH	% Octoxynol 40	% Sodium Diclofenac
6	1.0	0.05
7	1.0	0.05
8	0.5	0.05
8	1.0	0.05

After a minimum of 30 days storage at 22° C only clear and transparaent solutions have been obtained under the following experimental conditons:

pH	% Octoxynol 40	% Sodium Diclofenac
6	1.0	0.05
7	1.0	0.05
7	0.5	0.05
8	0.25	0.05
8	0.5	0.05
8	1.0	0.05
8	1.0	0.10

The rest of the formulations studied have not offered clear and transparent solutions, either because they have not been obtained at zero time or because precipitacions have appeared during the storage. It must also be pointed out that in the claims of the Fu and Lidgate Patent, the pH is specified as 7.4 ± 0.4 for formulas covered by the same, and following the results obtained, it is observed that pH 7, and even at 22°C and with the highest surfactant concentration, claimed in EP 0.390.071 Al, a clear and transparent solution cannot be obtained when using a 0.1% sodium Diclofenac and a 0.3% Tobramycin, concentrations generally used in Ophthalmology.

In general, the results obtained demonstrate a different behaviour between the Ketorolac and the Diclofenac, manifesting the existance of an interaction between the sodium Diclofenac and the Tobramycin. These differences could be explained by studying the special characteristics of the Diclofenac, such as has been referenced by various authors (11, 15). In this way, an ion interaction could be established between the Tobramycin and the sodium Diclofenac, similar to the one established between the derivates of quaternary ammonium and other non steroidal antiinflammatory agents, and a hydrophobic interaction, also between the Tobramycin and the sodium Diclofenac, which is characteristic of this latter component. The ion interaction is probably established between the sodium Diclofenac carboxyl group and the Tobramycin amine groups, due to which, and studying the respective pKs (14, 15), it is logical to think that the pH values used in the ophthalmic solutions, the pharmaceutically acceptable derivates of the Diclofenac and of the Tobramycin also present the same interaction.

Experimental conditions are proposed in the present invention, which permit the joint maintenance in solution of Diclofenace and Tobramycin in the concentrations generally used in Ophthalmology, solving the problems detected when reproducing Patent EP 0.390.071 Al, when preventing the formation of interactions between Diclofenac and Tobramycin.

Besides which, the experimental conditons described, allow the incorporation to the formulation, when it is believed necessary, of quaternary ammonium derivates as preservatives, since the same also prevent the interaction between said compounds and Diclofenac. The experimental conditions proposed allow the obtention of solutions which are clear, transparent, stable, well tolerated and therapeutically efficient and which together contain Diclofenac and Tobramycin, preventing the limitations of the previously described patents (Patents EP 0.390.071 AL, EP 0.306.984 B1, and USP 4.829.088), which, since they do not consider the establishment of the interaction between said components, do not permit the obtention of a formulation of Diclofenac and Tobramycin throughout all the scope of their claims, with the requirements necessary for this type of preparation.

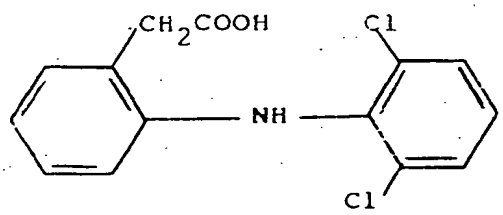
DETAILED DESCRIPTION OF THE INVENTION

The present invention refers to a solution of a non steroidal antiinflammatory agent, the Diclofenac, an antibiotic of the family of the aminoglycosides, the Tobramycin, and a solubilizing agent for its topic use in ocular and otic inflammatory processes which are presented together with infection.

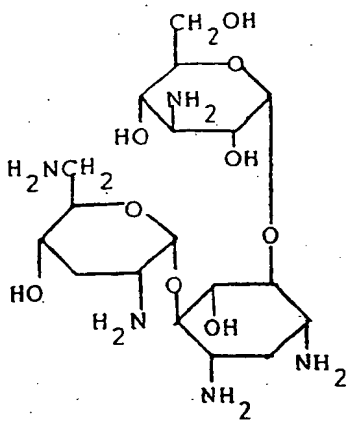
The ocular pathological processes which may be treated with the formulations described in the present invention are conjunctivitis or any other ocular trauma caused by an accident or a surgical operation. Additionally, the ocular inflammations and infections may also be treated with the formulations described in the present invention.

Likewise, with the formulations described in the present invention, diverse otic pathological processes may be treated, such as for example, external otitis. Moreover, the otic inflamations and infections may also be treated with the formulations described in the present invention.

Diclofenac is a non steroidal antiinflammatory agent which is chemically known as orto(2,6-dichlorophenyl) aminophenylacetic acid. The Diclofenac presents structural formula (I):



Tobramycin is an antibacterian agent, belonging to the family of the aminoglycosides, water soluble, and chemically kinwon as 4-[2,6-diamino-2,3,6-trideoxy-alpha-D-glycopiranosyl]-6-[3-amin-3-deoxy-alpha-D-glycopiranosyl]-2-deoxystreptamine. The Tobramycin presents structural formular (II):



Tobramycin presents a wide spectrum of action, versus both Gram positive and versus Gram negative organisms. The main susceptible microorganisms are Sthaphylococus aureus, Sthaphylococus epidermidis, Streptococus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae, Morganella morganii, Haemophilius influenzac, haemophilius aegyptius, Moraxela lacunata and Acinetobacter calcoaceticus.

Moreover, the present invention includes the isomers, derivatives and pharmaceutically acceptable salts of the Diclofenac and of the Tobramycin

In accordance with the present invention, the resultant combination includes the equivalence to a value comprised within a 0.001 and a 0.14% , obtained from the Diclofenac itself, or from a pharmaceutically acceptable derivate thereof, preferibly the equivalence to a value comprised within a 0.05 and a 0.10% obtained from Diclofena itself, or from a pharmaceutically acceptable derivate thereof, and the equivalence to a value comprised within a 0.001 and a 0.45% of Tobramycin obtained from Tobramycin itself, which is a pharmaceutically acceptable derivate thereof, preferibly, the equivalence to a value comprised within a 0.15 and a 0.35% of Tobramycin obtained from Tobramycin itself, or a pharmaceutically acceptable derivate thereof.

The solutions included in the present invention, incorporate, as solubilizing agents, the sobitane Steroids, the glycero-polyethlene-glycol Steroids and the Acid fats, or a mixture of said components. Typically, these compounds are used at levels comprised within a 3.0 and a 7.0%.

The compositions comprised in the present invention also include other compounds traditionally used in ophthalmic preparations, such as isotonilizer agents, pH damper substances, viscosizer agents, chelator agents and preservative agents.

The inclusion of any representative of the previously indicated compound groups depends on the characteristics which are required to be conferred to the final preparations. The selection of one or other compound depends on the physical, physico-chemical and chemical characteristics of the rest of the components in the formulation so as to obtain a stable, well tolerated and therapeutically efficient preparation.

In the following paragraphs, both in the descriptive part of the present memory as in the Note of the Claims, the percentages are expressed in weight/volume in those cases in which the resultant pharmaceutical form is a solution. If the resultant formulation is a hydrogel, the percentage is expressed in weight/weight.

As isotonizer agents may be cited, the sodium Chloride, the sodium Sulfate, the Glycol, the Manitol and the Sorbitol, among others. These compounds are used to achieve the tonics required in the preparations. Typically, these compounds are used at levels comprised within 0.4 and 75%.

As pH damper substances, may be included the Citrates, the Borates, the Phosphates, the Tris-(Hydroxymethyl)-aminomethane and the aminoacids such as Glycine and Lysine, the Glutamic Acid, the Arginine and the Aspartic Acid, among others. This type of products is introduced in the formulations to maintain the pH stable during the life time of the product and improve the tolerance when thus required by the product's use. Typically, these compounds are used at levels comprised within a 0.01 and a 3.0%

As viscosizing agents, which improve the time of residence of the product in its location of application, may be mentioned, among others, polyvynilic Alcohol, Polyvinylpyrrolidone, methylcelulose, Hydroxypropylmethylcelulose, among other. Typically these compounds ara used at levels comprised within a 0.01 and a 10.0%.

As chelator agents may be mentioned, among others, Citric Acid, Tetracetyc ethylendiamino acid (EDTA), the EDTA sodium salts and N,N,N'N'- tetracetic acid (EGTA). These compounds are included in order to eliminated the heavy metals from the solution and to improve the performance of the preservative agents. Typically, these compounds are used at levels comprised within a 0.01 and a 2.0%.

As preservative agents, in order to prevent the contamination of the product when the formulation is presented with a multidose format, may be included the derivates of quaternary ammonium (Benzalconium Chloride, cetylmethylammonium bromide, cetylpyridine chloride and Bencetone chloride), the organomecurial derivates (Timerosal, Phenyl mercuric acetates and Phenylmercuric nitrate), the Methyl and propyl p-Hydroxybenzoates and the sodium salts thereof, the Beta-phenylethylic alcohol, the Benzylic alcohol, the Phenylethylic alcohol and the Phenoxyethanol. The formulations of the present invention also include the mixture of said compounds. Typically, these compounds are used at levels comprised within a 0.0005 and a 5.0%, depending on the type of preservative agents selected.

Other optional excipients, which may be used depending on the final characteristics which are desired to be conferred to the preparation, may be the excipients generally used in the obtention of pharmaceutical hydrogels Poly(hydroxyethylmetacrylate), Poly(N-vinylpyrrolidone), Polyvinylic alcohol, Polymers of the Acrylic Acid, such as Carbopol, etc.). Typically, these compounds are used at levels comprised within a 0.01 and a 25.0%.

The characteristics of the selected components may condition the pharmaceutical form necessary for the obtention of a stable, well tolerated and therapeutically efficient preparation.

The pH of the formulations included in the present invention oscilates between 7 and 9. In order to adjust the pH of the formulations to the desired value, besides the damping agents previously indicated, acids (Chlorodydric, Sulphuric, etc) or bases (Sodium hydroxide, potassic hydroxide, etc) may be used.

The quantity of preparation which may be administered to the receptor animal depends on the nature of the latter (species, age, size) as well as the general health condition and the severity and type of illness it suffers. Though the schedule of the dose has been established by the doctor or veterinary, it is recommended that the application of the formulations included in the present invention be carried out from 1 to 4 times a day, depending on the characteristics of the formulation, instilling one or two drops each time.

The formulations included in the present invention may be packaged in containers generally used for this type of preparations.

In cases when its used so requires it, the formulations included in the present invention may be elaborated under sterile conditions.

The presence of Tobramycin, or of a pharmaceutically acceptible derivate thereof, does not affect the activity of the antiinflammatory agent used, neither does the presence of Diclofenac, or of a pharmaceutically acceptable derivate thereof, interfer in the antimicrobian activity of the antibiotic.

Using an adequate combination of the components described in the present invention, formulations are obtained with effective results, from the antimicrobian point of view, according to the criteria of the different pharmacopeias.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 (a) IR spectrum of the sodium Diclofenac (b), IR spectrum of the Tobramycin. (c) IR spectrum of the precipitated obtained from a formulation with 0.1% sodium Diclofenac, 0.3% Tobramycin, 0.01% BAC, 1.0% Octoxyno 40 and pH 8.0. Bands are observed at approximately 1.500 cm^{-1}, characteristic of the sodium Diclofenac carboxyl groups, and a band, at approximately 1.050 cm^{-1}, characteristic of the Tobramycin C-N and C-O groups.

Figure 2. DSC profile, obtained with the physical mixture (M) of sodium Diclofenac and Tobramycin and with precipitat (P) obtained from a formulation with 0.1% sodium Diclofenac, 0.3% Tobramycin, 0.01% BAC, 1.0% Octoxyno 40 and pH 8.0.

EMBODIMENTS OF THE INVENTION

The present invention is additionally represented by means of the following nonlimitative Examples of its scope.

EXAMPLE NO.1

Substance	Quantity for 100ml
Sodium Diclofenac	0.100 g
Tobramycin	0.300 g
Benzalconium chloride	0.010 g
Polysorbate 80	3.000 g
Boric acid	0.900 g
Sodium Tetraborate	0.450 g
EDTA Na_2	0.100 g
NaC1 c.s.p	300 m 0 s mo 1/ Kg
HC1 and/or Na OH c.s.p.	pH 8.4 0.4
Pure water x.s.p	100 ml

For the obtention of the ophthalmic solution, 80% water of the formulation is placed in an adequate container, adding the Benzalconium Chloride, the Boric Acid, the Tetraborate, the EDTA Na_2, the NaC1, the Polysorbate 80, the Tobramycin and the Sodium Diclofenac. The pH is adjusted with HC1 and/or Na OH, completing the volume with water and filtering the resultant solution through a filtration system of 0.22 micrometers, previously sterilized. The dose of the solution obtained is measured in adequate previously sterilized flasks.

EXAMPLE NO.2

Substance	Quantity for 100 ml
Sodium Diclofenac	0.100 g
Tobramycin	0.300 g
Benzalconium chloride	0.010 g
Polysorbate 20	3.000 g
Boric acid	0.900 g
Sodium tetraborate	0.450 g
EDTA Na_2	0.100 g
Na C1 c.s.p.	300 mosmo1/Kg
HC1 and/or Na OH c.s.p	ph 8.4 .4
Pure water c.s.p	100 ml

For the obtention of the ophthalmic solution, place 80% water of the formulation in an adequate container, adding the Benzalconium Chloride, the Boric Acid, the Tetraborate, the EDTA Na_2, the NaC1, the Polysorbate 20, the Tobramycin and the sodium Diclofenac. the pH is adjusted with HC1 and /or NaOH, completing the volume with water and filtering the resultant solution through a filtration system of 0.22 micrometers, previously sterilized. The dose of the solution obtained is measured in adequate previously sterilized flasks.

EXAMPLE NO.3

Substance	Quantity for 100 ml
Sodium Diclofenac	0.100 g
Tobramycin	0.300 g
Benzalconium Chloride Glycerol-polyethylenglycol	0.010 g
ricinoleate	3.500 g
Tromethamol	0.600 g
EDTA Na_2	0.100 g
Na C1 c.s.p.	300 mOsmo1/Kg
H_2SO_4 and/or NaOH c.s.p	ph 8.4 .4
Pure water c.s.p	100 ml

For the obtention of the ophthalmic solution, place 80% water of the formulation in an adequate container, adding the Benzalconium chloride, the Tromethamol, the EDTA Na_2, the NaC1, the glycerol-polyethylenglicol ricinoleate, the Tobramycin and the sodium Diclofenac. The pH is adjusted with H_2SO_4 and /or NaOH, completing the volume with water and filtering the resultant solution through a filtration system of 0.22 micrometers, previously sterilized. The dose of the solution obtained is measured in adequate previously sterilized flasks.

EXAMPLE NO.4

Substance	Quantity for 100 ml
Sodium Diclofenac	0.100 g
Tobramycin	0.300 g
Benzalconium Chloride	0.010 g
Polysorbate 80	3.000 g
Hydroxypropylmethylcelulose	0.300 g
Boric Acid	0.900 g
Sodium Tetraborate	0.450 g
EDTA Na_2	0.100 g
NaC1 c.s.p.	300 m0smo1/ Kg
HC1 and/or N aOH c.s.p.	pH 8.4±0.4
Pure water c.s.p	100 ml

For the obtention of the ophthalmic solution, place 805 water of the formulation in an adequate container, adding the Benzalconium chloride, the Hydroxypropylmethylcelulose, the Boric Acid, the Tetraborate, the EDTA NA_2, the NaC 1, the Polysorbate 80, the Tobramycin and the sodium Diclofenac. The pH is adjusted with HC1 and/or NaOH, completing the volume with water and filtering the resultant solution through a filtration system of 0.22 micrometers, previously sterilized. The dose of the solution obtained, is measured in adequate previously sterilized flasks.

EXAMPLE NO. 5

Substance	Quantity for 100 ml
Sodium Diclofenac	0.100 g
Tobramycin	0.300 g
Benzalconium Chloride	0.010 g
Polysorbate 20	3.000 g
Hydroxyethylcelulose	0.500 g
Boric acid	0.900 g
Sodium tetraborate	0.450 g
EDTA Na_2	0.100 g
NaC1 c.s.p.	300 m0smol (Kg
HC1 and/or N aOH c.s.p.	pH 8.0±0.4
Pure water c.s.p	100 ml

For the obtention of the ophthalmic solution, place 80% water of the formulation in an adequate container, adding the Benzalconium Chloride, the Hydroxyethylcelulose, the Boric Acid, the Tetraborate, the EDTA Na_2, the NaC1, the Polysorbate 20, the Tobramycin and the Sodium Diclofenac. The pH is adjusted with HC1 and/or NaOH, completing the volume with water and filtering the resultant solution through a filtration system of 0.22 micrometers, previously sterilized. The dose of the solution obtained, is measured in adequate, previously sterilized flasks.

Claims

1. Ophthalmic solutions based on Diclofenac, and Tobramycin, for topic ophthalmic and otic use, characterized in that it presents a pH comprised within 7 and 9 and in that it comprises:

   - the equivalent to a value between 0.001-0.14% Diclofenac; obtained from Diclofenac itself, or from an isomer, or from a derivate or one of the pharmaceutically acceptable salts thereof;
   - the equivalent to a value between 0.001-0.45% of Tobramycin, obtained from Tobramycin itself or from an isomer, or a derivate or one of the pharmaceutically acceptable salts thereof;
   - 3.0 -7.0% of a solubilizing agent, and
   - optionally, 0.4-7.5% of a isotonizing agent;
   - optionally, 0.01- 3.0% of a pH damper agent;
   - optionally, 0.01-10.0% of a viscosizing agent;
   - optionally, 0.01- 2.0% of a chelator agent;
   - optionally, 0.0005-0.015% of a preservative agent of the quaternary ammonium group;
   - optionally, 0.0005-0.0065% of a preservative agent of the mercurial derivates group;
   - optioanlly 0.05 -0.5% of a preservative agent of the methyl and propyl p-Hydroxybenzoate group and the sodium salts thereof;
   - optionally, 0.05-0.75% of Phenylethylic alcohol or Beta-phenylethylic alcohol as preservative agent;
   - optionally 0.05-5.0% of Benzylic alcohol as preservative agent;
   - optionally 0.05-1.0% of Phenoxyethanol as preservative agent, and
   - optionally 0.01-25% of an excipient used for pharmaceutical hydrogels.

2. A solution according to claim 1, characterized in that the solubilizing agent is selected from among the sorbitane Sters, the glycerolpolyethyleneglycerin Sters, and fat acid group, or a mixture of said components.

3. A solution according to claim 1, characterized in that the isotonizer agent is selected from the group formed by the Sodium Chloride, the Sodium Sulphate, Glycerol, Manitol and Sorbitol.

4. A solution according to claim 1, characterized in that the damping agent is selected from the group formed by the Acetates, the Citrates, the Borons, the Phosphates, the Tris(hydroxymethyl)-aminomethane, and the aminoacids, such as Glycerines, Lysine, Glutamine acid, Arginine and Aspartic acid.

5. A solution according to claim 1, characterized in that the viscosizer agent is selected from the group formed by the Polyvinyl alcohol, the Polyvinylpyrrolidone, the Methylcelulose, the Hydroxypropylcelulose, the Hydroxiethylcelulose, the Carboxymethylcelulose and the Hydroxypropylmethylcelulose.

6. A solution according to claim 1, characterized in that the chelator agent is selected from the group formed by the citric acid, the tetracetic ethylendiaminoacid (EDTA), the EDTA sodium salts and the N,N,N',N'-tetracetic Acid (EGTA).

7. A solution according to claim 1, characterized in that the preservative agent is selected from among the group of quaternary ammonium derivates (Benzalconium chloride, cethylmethylammonium Bromide, Cetylpyridine Chloride and Benzeton Chloride), the organomercurial derivates (Timerosal, Phenylmercuric Acetate and Phenylmercuric nitrate), or a mixture of said components and of the other said preservative agents as optional in claim 1.

8. A solution according to claim 1, characterized in that the forming excipient of pharmaceutical hydrogels is selected from the group formed by the Poly (Hydroxiethylmetacrylate), the Poly(N-vinylpyrrolidone), the Polyvinylic alcohol and the Acrylic Acid Polimers, such as Carbopol.

9. Application of the formulations of previous claims 1 to 8 for the manufacturing of medicines to the treatment of ocular inflammations and/or infections.

10. Application of the formulations of previous claims 1 to 8 for the manufacturing of medicines to the treatment of otic inflammations and/or infections.

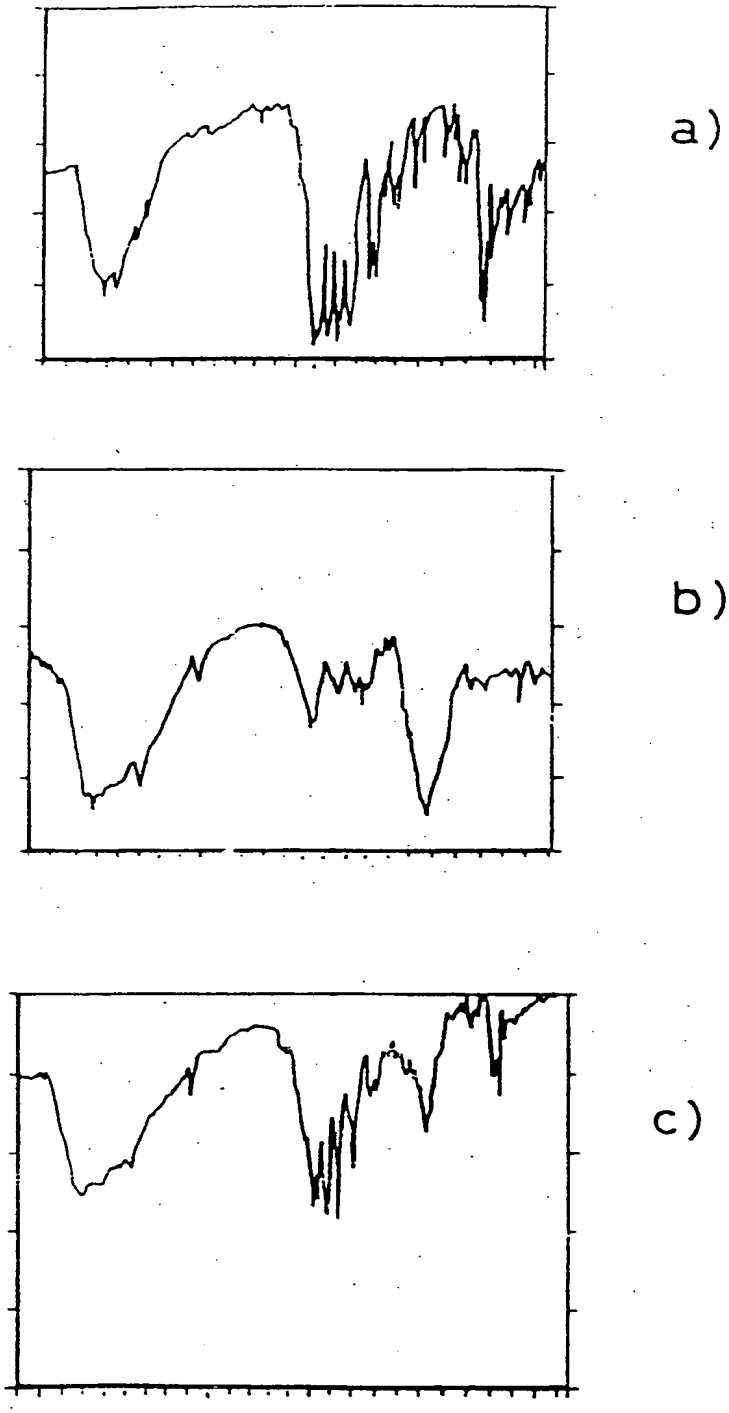


FIG.1

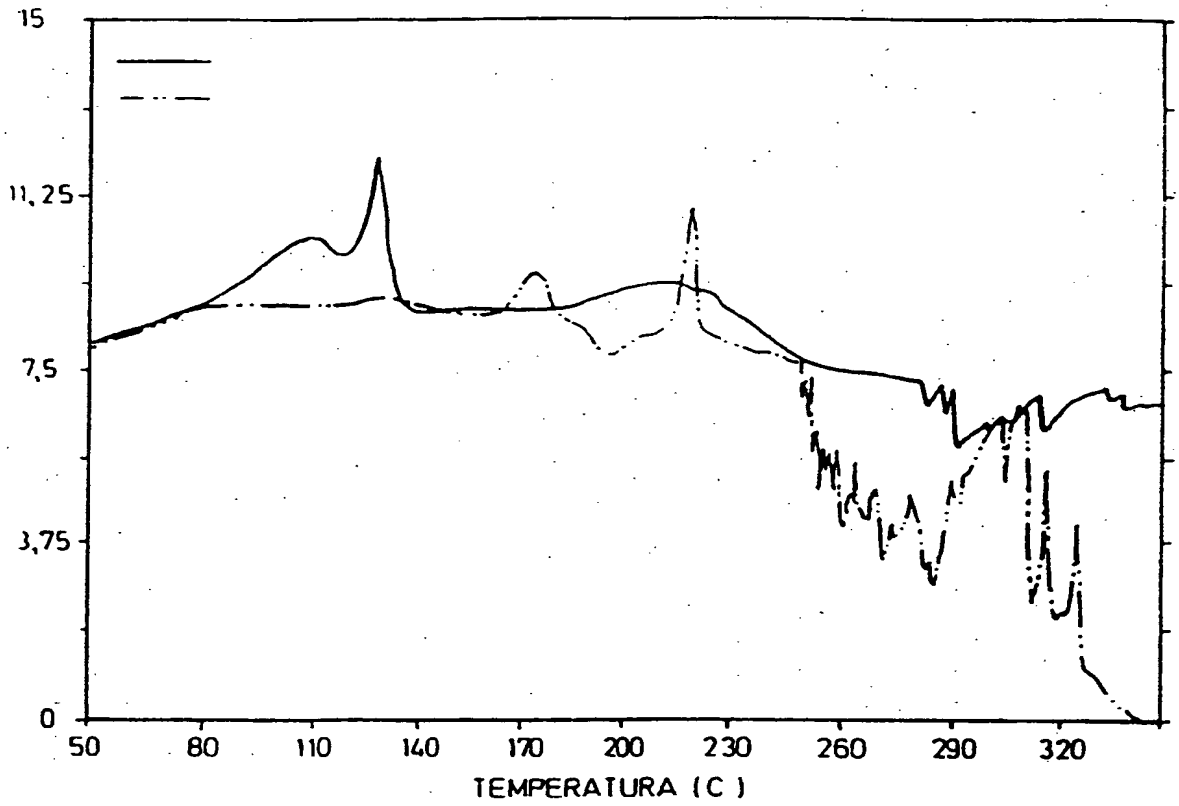

15
11,25
7,5
3,75
0
50
80
110
140
170
200
230
260
290
320
TEMPERATURA (C)

FIG.2

INTERNATIONAL SEARCH REPORT

Inter. al Application No
PCT/ES 94/00084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 390 071 (SYNTEX) 3 October 1990 cited in the application see the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 January 1995	17.01.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)